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Case report

High pseudotumor cerebri incidence in tretinoin and arsenic treated acute promyelocytic leukemia and the role of topiramate after acetazolamide failure

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ABSTRACT

Dual differentiation therapy with arsenic trioxide and tretinoin (all-*trans*-retinoic acid; ATRA) for the management of low and intermediate risk acute promyelocytic leukemia has recently been recommended by the National Comprehensive Cancer Network. Some less common toxicities of the combination may have yet to be fully realized. Of ten patients we have treated thus far, five (50%) have developed pseudotumor cerebri. In one patient, temporary discontinuation of ATRA and initiation of acetazolamide controlled symptoms. In four patients, topiramate was substituted for acetazolamide to relieve symptoms and allow ATRA dose re-escalation. We conclude that providers should monitor for pseudotumor cerebri and consider topiramate if acetazolamide fails.

1. Introduction

Acute promyelocytic leukemia (APL) is an aggressive myeloid malignancy defined by the presence of the PML-RARα fusion gene produced by a translocation between chromosomes 15 and 17. Through risk stratification and incorporation of tretinoin (all-*trans*-retinoic acid; ATRA) into treatment, patient outcomes have drastically improved with complete response (CR) rates reaching $>90\%$ when combined with chemotherapy [1–3]. Most recently, dual differentiation therapy with ATRA and arsenic trioxide (ATO) (Table 1), has become a recommended first-line regimen by the National Comprehensive Cancer Network for the management of patients with low/intermediate risk APL (white blood cell (WBC) count $<10\times10^9$/L), or patients with high risk disease who are unable to receive anthracycline-based chemotherapy [4]. ATO binds to the PML end of the fusion protein resulting in apoptosis of APL cells [5]. A randomized controlled trial by Lo-Coco et al. [6] demonstrated complete remission rates of 100% with dual differentiation therapy, proving non-inferiority of the ATO-ATRA combination over ATRA plus chemotherapy in the management of low/intermediate risk APL.

Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension, is a condition characterized by an increase in intracranial pressure, without cerebrospinal fluid (CSF) abnormalities or radiological evidence of other intracranial pathology (hydrocephalus, mass, structural or vascular lesion) [7]. PTC following ATRA administration for APL has been well described [8–26]. However, reports of PTC resulting specifically from dual differentiation therapy are currently lacking, and there is a paucity of evidence describing management of this condition specifically in patients with APL, where continuation of therapy is necessary for optimal clinical outcomes.

Although the exact mechanism of ATRA induced PTC is currently unknown, a variety of medications are used in its management including carbonic anhydrase inhibitors, diuretics, corticosteroids, and analgesics. Acetazolamide, a carbonic anhydrase inhibitor, is the most commonly used agent in the management of non-drug induced PTC and is thought to work through reduction of CSF production. More recently, the anticonvulsant topiramate has been viewed as an attractive treatment option for idiopathic PTC given its activity as a carbonic anhydrase inhibitor (mostly at receptor subtypes II and IV) and its efficacy as a migrainolytic [27–29]. The precise mechanism of both migrainolysis and anti-epileptic efficacy is unknown, however the drug is known to antagonize sodium channels, augment the effect of gamma-aminobutyrate (GABA) at receptor subtype A, and antagonize the AMPA/kainate subtypes of the glutamate receptors [30].

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Table 1
Schedule of induction and consolidation components of ATO–ATRA dual differentiation regimen [6,32].

Induction[a]		
ATRA[b]	AND	ATO[b]
45 mg/m^2/day divided twice daily in equal doses		0.15 mg/kg/day in 500 mL normal saline intravenous over two hours
Bone marrow biopsy on day 28: If $<5\%$ blasts and no abnormal promyelocytes, discontinue ATRA and ATO until occurrence of CR[c]. Biopsy repeated weekly until criteria for drug discontinuation met.		
Consolidation		
ATRA[b]	AND	ATO[b]
45 mg/m^2/day divided twice daily in equal doses for two weeks every 4 weeks for a total of 7 cycles		0.15 mg/kg/day in 500 mL normal saline intravenous over two hours 5 days a week for 4 weeks every 8 weeks for a total of 4 cycles

[a] On days 1–5 of induction therapy, all patients received therapy with methylprednisolone 48 mg PO daily for differentiation syndrome prophylaxis.
[b] ATRA, All-*trans* retinoic acid; ATO, arsenic trioxide.
[c] CR, complete response defined by neutrophil and platelet counts greater than 1×10^9/L and 100×10^9/L, respectively, together with the noted marrow findings.

Table 2
Disease characteristics of patients developing pseudotumor cerebri (PTC) on dual differentiation therapy.

Case	At diagnosis of APL					At diagnosis of PTC		PTC Symptom Onset
	Risk category[a]	WBC[b] (cells/L)	Plt[b] (cells/L)	PMC[b] (%)	PML-RAR-α FISH[b] (%+cells)	ICP[b] (cm H_20)	BMI[b] kg/m^2	# of days after initiation of ATO–ATRA
1	Intermediate	5×10^9	39×10^9	93	90	35	32.1	Induction: day 1
2	Low	0.9×10^9	49×10^9	6	83	39	30.2	Induction: day 1
3	Low	2.5×10^9	77×10^9	66	11	28	37.1	Induction: day 1
4	Low	5.8×10^9	41×10^9	26	92	36	28.5	Induction: day 31
5	Intermediate	3.4×10^9	29×10^9	44	85	27	23.6	Consolidation[c]: Cycle 1, day 3 Cycle 2, day 3 Cycle 3, day 1

[a] "Low" risk defined platelet count $>40 \times 10^9$/L and white blood cell count $<10 \times 10^9$/L; "Intermediate" risk defined as platelet count $<40 \times 10^9$/L, and white blood cell count $<10 \times 10^9$/L.
[b] WBC, white blood cell count; Plt, platelet count; PMC, promyelocytes; FISH, fluorescence *in-situ* hybridization; ICP, intracranial pressure; and BMI, body mass index.
[c] A "cycle" of consolidation refers to the eight week cycles of arsenic trioxide therapy (total of four cycles).

From November 2012, through January 2014, ten patients with low or intermediate risk APL received upfront dual differentiation therapy with the ATO–ATRA combination [4]. Out of these ten patients, we describe five (50%) cases of PTC which occurred following the initiation of dual differentiation therapy and their clinical courses, with an emphasis on our experience with the substitution of topiramate in place of acetazolamide in non-responders.

2. Case 1

A 54 year old African American male was transferred to RPCI where workup revealed a diagnosis of APL (Table 2) and dual differentiation therapy was subsequently initiated (Table 1). That same evening, he complained of severe headache that was out of the ordinary for him with no other symptoms. Of note, he was also receiving concomitant diltiazem CD 180 mg daily, a medication known to inhibit CYP3A4 [31]. A head CT scan was without any abnormalities, and a lumbar puncture (LP) revealed an elevated intracranial pressure (ICP) of 35 cm H_20. ATRA was interrupted, and acetazolamide was started at 250 mg orally twice daily. After two days, his headache resolved and ATRA was restarted with an 80% dosage reduction. Headaches resumed upon ATRA reintroduction. However, therapy was continued, and acetazolamide was increased to 500 mg orally twice daily.

Acetazolamide was unable to relieve the headaches and was discontinued. Topiramate was initiated, with subsequent headache relief noted at a dose of 100 mg orally twice daily. With this therapy, ATRA was able to be re-titrated to a maximum of 40 mg orally twice daily (80% of initial dose) over two weeks until PTC recurred. Following therapeutic lumbar puncture, ATRA was resumed at 30 mg orally twice daily. A topiramate dose of 150 mg orally twice daily was needed to control symptoms for the remainder of induction. At no point during treatment was ATO interrupted. Upon discharge, the patient was prescribed topiramate 100 mg orally twice daily to begin the day prior to starting ATRA consolidation. He completed consolidation as planned. Four months following therapy completion, he remains in CR.

3. Case 2

A 24 year old Caucasian male with no past medical history was transferred to RPCI. Workup at revealed APL (Table 2) and ATO–ATRA induction was initiated (Table 1). The following day, the patient complained of headaches that had been occurring since his first dose of ATRA and were poorly controlled with opiates. Additionally, the patient was experiencing nausea, which was relieved with ondansetron. At that point, acetazolamide at a dose of 250 mg orally twice daily was added to be taken half an hour prior to ATRA dosing.

After three days, the patient experienced mild relief of headaches. Reduction of the ATRA dose by 50% further relieved his pain. However, he began feeling increasingly nauseous with vomiting episodes for twenty-four hours. A brain CT showed no abnormalities, and an LP was diagnostic for PTC with an ICP of 39 cm H_20. ATRA was held for three doses and acetazolamide continued. Once reinitiated, ATRA was titrated up to 30 mg orally twice daily over five days with acetazolamide also increased to 500 mg orally twice daily. Despite acetazolamide, he began to complain of headaches again and was subsequently changed from acetazolamide to topiramate 100 mg orally twice daily. ATRA was then titrated over three days up to full dose (50 mg orally in the morning and 60 mg

orally in the evening) and was continued, with topiramate, for the remainder of induction. At no point during induction was ATO interrupted. At the time of reporting, he remains in CR following the completion of consolidation therapy with maintenance ATRA 50 mg orally twice daily for seven days every other week.

4. Case 3

A 45 year-old Caucasian male with a history of migraines presented to RPCI for pancytopenia. Workup revealed APL (Table 2) and the patient was admitted to begin ATO–ATRA (Table 1). Following his first dose of ATRA, the patient developed severe headaches with 10/10 intensity. CT of the brain was negative for any abnormality, and he was initiated on hydromorphone as needed for two days, with minor relief. At this time, a diagnostic LP revealed an ICP of 28 cm H_20. He was then initiated on acetazolamide, which was increased to 500 mg orally twice daily, while continuing full-dose ATRA. He began to also complain of severe back pain requiring hydromorphone via patient controlled analgesia. With only minor pain relief, the ATRA dose was reduced by 50% and subsequently held for two additional days.

Despite these measures, the patient continued to have pain, and his acetazolamide was switched to topiramate, which produced marked improvement in his head and back aches over a four-day period at a dose of 100 mg orally twice daily. Due to high opioid requirements, hydromorphone was converted to methadone for chronic management. After reinitiating ATRA at a reduced dose, it was re-titrated up to full-dose ATRA over ten days and continued for the remainder of his induction course. Using up to 150 mg twice daily of topiramate, his methadone was tapered down as back pain improved and headaches disappeared. Upon discharge, he received a prescription for topiramate to be taken during ATRA periods of consolidation. With doses of 200 mg orally twice daily, his methadone was discontinued and switched to hydromorphone as needed for pain control. He is currently in his third course of consolidation and remains in CR.

5. Case 4

A 59 year old Caucasian male with a history of chronic renal insufficiency was transferred to our intensive care unit from an outside hospital, intubated secondary to respiratory failure and severe mucositis. He arrived on multiple broad spectrum antibiotics for treatment of healthcare associated pneumonia and possible invasive fungal infection. He was found to have APL (Table 2) and was started on ATO–ATRA induction (Table 1). ATRA was administered as a compounded suspension down a nasogastric tube during intubation. He continued to be intubated for the first week of the dual differentiation therapy and was extubated on day ten of his admission. Due to renal failure of unclear etiology requiring hemodialysis, ATO was dosed every 48 h for the first two weeks of therapy until normalization of renal function. At day 28, a bone marrow biopsy revealed persistent disease, and a repeat marrow was planned for one week later.

Thirty one days after initiation of induction, this patient began to experience 8/10 intensity headaches accompanied by nausea. Pain was unrelieved by oxycodone. A diagnostic LP revealed an elevated ICP (Table 1) without CSF abnormalities. ATRA was held and acetazolamide started at 500 mg orally twice daily. After holding three doses of ATRA, headaches completely resolved and ATRA was then restarted at 50% of the original dosage. His ATRA was able to be titrated up to 67% of the original dose, which he continued for the remainder of induction. He was discharged with a prescription for acetazolamide 250 mg orally twice daily to take during ATRA consolidation. After initiation of consolidation cycle 1, he was admitted for renal insufficiency and metabolic acidosis secondary to acetazolamide treatment. Since then, he has been taking sodium bicarbonate tablets 650 mg orally twice daily with acetazolamide. At the time of this writing, he is currently receiving cycle 2 of consolidation and remains in CR.

6. Case 5

A 62 year old Caucasian male with a history of thyroid cancer was transferred to RPCI for further workup of pancytopenia, fevers, and flu-like symptoms. Work up revealed APL (Table 2). He successfully completed induction with dual differentiation therapy without interruption or development of PTC. A bone marrow biopsy on day 28 met criteria for drug discontinuation, and the patient was discharged home. Two weeks later, upon obtaining CR, he began consolidation (Table 1).

Three days into his first cycle of consolidation, the patient presented with complaints of headaches that were unrelieved by oxycodone. The patient was initiated on acetazolamide 250 mg orally twice daily to be taken with ATRA, which led to minimal headache relief. A diagnostic LP revealed PTC (Table 1). As a result, ATRA was held, acetazolamide discontinued, and topiramate 50 mg orally twice daily initiated. He continued topiramate for ten days until complete resolution of headaches. At the start of his next two-week ATRA period, his ATRA was reinitiated at 50% of his original dose, and topiramate switched back to acetazolamide 250 mg orally twice daily for headache prophylaxis.

Four weeks later, on the first day of cycle three, the patient began to develop headaches again that failed to respond to oxycodone and acetazolamide 500 mg orally twice daily. Again, his ATRA was held, acetazolamide discontinued, and topiramate reinitiated at 50 mg orally twice daily. After complete resolution of his headaches, ATRA was reinitiated at 50% of his previous dose and continued, along with topiramate, for the remainder of his consolidation. Of note, the patient was receiving omeprazole, a CYP3A4 inhibitor, throughout the duration of his consolidation therapy. He currently remains in remission four months after completion of consolidation therapy.

7. Discussion

Dual differentiation therapy has revolutionized the management of APL with comparable CR rates to ATRA plus chemotherapy with decreased risk of many adverse events typically associated with anthracyclines [6]. Despite the reduction shown in oral, hematologic, and infectious complications, the combination of ATO–ATRA is by no means risk free. Treatment with dual differentiation has been associated with significantly higher rates of QTc prolongation and hepatotoxicity compared to ATRA with idarubicin [6]. Although PTC has gone unreported in studies demonstrating the efficacy of the ATO–ATRA combination [6,32,33], our report suggests a significant incidence of PTC amongst APL patients being managed with this combination. Of the ten patients identified as having received dual differentiation therapy, five developed PTC, making our incidence 50%, an alarming rate. It is unclear why our patient population developed such a high incidence of PTC. We report the management of our first 10 patients receiving dual differentiation therapy, however it is possible that the incidence may become diluted once we have treated a larger number of patients. In addition, our team may have become more vigilant in screening for PTC and had a lower threshold for doing a LP upon symptom development given our previous patient's experiences with PTC from ATO-ATRA. A third possible reason may be related

to under reporting of this complication of dual differentiation therapy.

The diagnosis of PTC, based on the Modified Dandy Criteria, is made when a patient exhibits an elevated LP opening pressure above 25 cm H_20 with normal CSF composition and radiologic findings, and no other explanation for the rise in intracranial pressure [6]. The most common presenting symptom occurring in nearly all patients is headache. Other signs and symptoms known to occur to a lesser degree include nausea, vomiting, transient visual disturbances, diplopia, papilledema, and pulsatile tinnitus. Symptoms usually develop within 14 days of ATRA initiation [7]. In our practice, patients receiving ATRA who report persistent headache that is poorly controlled with opiates or other commonly used analgesics typically undergo a LP to investigate the possibility of PTC. The LP is usually considered after more than 24 h of symptoms, or sooner if the patient reports visual disturbance in addition to headache. Of the five cases of PTC presented in this report, three cases developed symptoms following their very first dose of ATRA. However, in two patients, development of PTC was delayed (see Table 1), highlighting that PTC can occur at any point during therapy.

PTC secondary to ATRA administration for APL has been well described in the literature through case reports in both the pediatric and young adult populations [7–26] and, among adults, has been most often associated with obese women of child-bearing age [34]. However, all patients described in this report were males with a wide age range and body mass indexes (BMIs) consistent with an overweight (BMI 25.0–29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) stature. Given the remarkable incidence of PTC in our patients receiving ATO-ATRA, it is possible that ATO may foster the development of this condition in APL patients. PTC has been reported previously in a 21-year old woman receiving ATO consolidation therapy for APL without concurrent ATRA [35]. The mechanism for ATO induced PTC has not been identified. However, the primary mechanisms of agents known to cause PTC involves the alteration of CSF absorption by effects on either the pressure differential between the central nervous system and venous blood (increasing inflow), or the arachnoid villi (reducing outflow) [36]. The suggested mechanism of ATRA induced PTC is a toxic pathophysiological interaction between vitamin A derivatives and lipid constituents of the choroid plexus and arachnoid villi, resulting in inhibited CSF absorption and an increase in intracranial pressure [37].

Treatment of this condition is necessary to prevent the primary complication, blindness, secondary to progressive optic disc swelling and atrophy [38]. Management strategies aim to lower intracranial pressure through one or more of the following: removal of the offending agent (discontinuation of ATRA), removal of CSF (therapeutic LPs), inhibition of CSF production (acetazolamide), diuresis (mannitol, glycerin, furosemide), and analgesia. Topiramate has more recently been described as a treatment option for PTC [28]. This agent is primarily used in the management of epilepsy, but is also indicated for migraine prophylaxis [30]. Migraine headaches share similar pathophysiological mechanisms with seizures, including abnormal function of voltage-gated sodium and calcium channels, reduced GABA mediated inhibition, and increased glutamate-mediated excitation, many of which may be antagonized by topiramate [30,39]. It is unclear why topiramate was effective after the failure of acetazolamide in our patient population. Our patients received a maximum of 1 g of acetazolamide daily (administered as 500 mg twice daily). The optimal dose of acetazolamide for management of PTC is unknown, however a recent publication in patients with idiopathic PTC administered an initial total daily dose of 1 g and titrated up weekly as tolerated to a maximum daily dose of 4 grams [40]. It is unclear if our patients would have had better symptom control on higher doses of acetazolamide. We did not repeat LPs to assess the actual reduction in opening pressure after initiation of topiramate. Given that ATRA may cause headache even in the absence of ICP changes, it is possible that topiramate is simply better at managing such drug induced headache than acetazolamide is, and that it is not necessarily any better at decreasing ICP. Such a theory may be supported by the efficacy of topiramate in managing migraine headache. It is also possible that the additional mechanisms of action of topiramate, as compared to acetazolamide, may have played a role in further reducing intracranial pressure lower than that able to be obtained with acetazolamide alone, thus resulting in improved symptom control.

Evidence of the efficacy of topiramate in PTC has been reported in the literature [41,42]. The largest study, an open-label trial by Celebisoy and colleagues [41], demonstrated the non-inferiority of topiramate to acetazolamide in the management of idiopathic intracranial hypertension in a population consisting primarily of women of child-bearing age. Patients with secondary causes of PTC, such as medications, were excluded from this analysis. Although one of our five cases was successfully managed with ATRA interruption and acetazolamide treatment alone, the remaining four experienced symptom relief only after topiramate was utilized. Three of four patients receiving topiramate were being closely monitored in the inpatient setting. Additionally, three patients were able to safely receive topiramate as outpatients with regularly scheduled follow-up.

Metabolism of ATRA occurs through the CYP450 system. Co-administration of agents that inhibit CYP3A4, CYP2C8, and CYP2C9 has been implicated to increase serum ATRA levels [43]. Theoretically, these interactions could potentiate PTC in patients managed with differentiation therapy. ATO is primarily metabolized through methylation. Methyltransferases responsible for this reaction are not members of the CYP450 system, and formal drug interaction studies with this agent have not been conducted [44]. Standard protocol at our institute dictates that neutropenic patients receiving dual differentiation therapy are to receive fungal prophylaxis with micafungin. Although azole antifungals were not used in the patients included in our report, two cases were receiving CYP3A4 inhibitors (diltiazem and omeprazole) during ATO–ATRA therapy and at onset of PTC symptoms. No other interacting medications were noted.

In conclusion, our report suggests a high frequency of PTC (50%) associated with dual differentiation therapy for patients with low to intermediate risk APL. Our data also represents the largest case series to date supporting the use of topiramate for the management of this condition. Clinicians utilizing dual differentiation therapy for the management of low/intermediate risk APL should be aware of the increased potential for development of this condition and the appropriate use of agents, including topiramate, to reduce intracranial pressure, relieve symptoms and, importantly, permit ATRA re-initiation and dose escalation.

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